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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER: W ~~D IX 1613~~

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ART UNIT	PAPER NUMBER
ULM;J	24

CATHRYN CAMPBELL
CAMPBELL AND FLORES
4370 LA JOLLA VILLAGE DRIVE
SUITE 700
SAN DIEGO CA 92122

1646
DATE MAILED: 10/22/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/12/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-5, 7, 16-32, 66-75, 77 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-5, 7, 16-32, 66-75, 77 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

1) Claims 1 to 5, 7, 16 to 32, 66 to 75 and 77 are pending in the instant application. Claims 1, 16, 26, 28 and 32 have been amended and claims 8, 33 and 76 have been canceled as requested by Applicant in Paper Number 20, filed 14 June of 1999.

2) Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

3) The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4) Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 14 June of 1999 has been entered.

5) 37 C.F.R. § 1.84(U)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by **the same number followed by a capital letter**. The instant application contains a number of partial views of figures on multiple sheets which are intended to be combined to form complete views. For example, the figures labeled 2-1 and 2-2 should be labeled 2A and 2B. Once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(U)(1), Applicant is required to file an amendment to change the Brief Description of the Drawings and the rest of the specification accordingly. If, for example, Figure 2 is divided into Figures 2A and 2B then the Brief Description and all references to this figure in the specification must refer to Figures 2A and/or 2B.

6) Claims 1 to 5, 7 and 77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. These claims require the construction of a DNA encoding a fusion protein comprising the gene VIII gene product of a filamentous bacteriophage, wherein the fusion protein is expressed on the surface of a cell. The instant specification, as filed, did not describe such a DNA nor does it provide the guidance needed to make it. As indicated by the text on page 7 of the instant specification, "[t]he gVIII-Hc fusion protein therefore anchors the assembled Hc and Lc polypeptides on the surface of M13". At no point does the instant specification actually describe a method which leads to the expression of a gVIII fusion protein on the surface of any cell. As indicated by the section of the specification entitled ""**Screening of Surface Expression Libraries**", beginning on page 32, the gVIII fusion proteins of the instant invention are expressed on the surface of M13 filamentous bacteriophage, which are not cells.

7) Claims 1 to 4, 7, 16 to 19, 21 to 29, 31, 32, 66 to 75 and 77 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is not enabling for the production of first and second DNA sequences encoding the functional portions of any "heteromeric receptor" protein other that the variable heavy and variable light chains of an antibody or T cell receptor molecule, or for the production of a vector comprising sequences "necessary" for the expression of any other "heteromeric receptor" protein on the surface of a filamentous bacteriophage. Because the prior art

described the successful expression of variable heavy and variable light immunoglobulin molecules both as Fab molecules in bacteria and as single chain antibodies on the surface of bacteriophage by expressing those single chain antibodies as fusion proteins comprising a coat protein from the bacteriophage on which they were expressed, a practitioner knows that such proteins can be expressed in this fashion, even in the absence of the instant specification. However, the art of molecular biology does not recognize immunoglobulins as "receptor" proteins because they do not directly transduce a signal in a cell expressing them upon binding to a ligand. Further, because the extracellular domains of T cell receptors were known to be structurally analogous to immunoglobulins and are naturally found anchored to the surface of a cell by as single transmembrane domain an artisan would reasonably conclude that the variable domains from these protein could be expressed as a single chain protein on the surface of a bacteriophage in the same fashion as a single chain antibody. However, it is well known in the art that the majority of non-immunoglobulin proteins which would be encompassed by the term "heteromeric receptor" belong to the family of receptor protein complexes known as ligand gated ion channels. These receptors exist in nature as heteropentameric structures composed of different subunits and serve as receptors for such ligands as glutamate, acetylcholine, glycine and gama amino butyric acid. Each of the different subunits of these pentameric structures is believed to comprise three extracellular domains, four transmembrane domains and two cytoplasmic domains. The entire functional receptor complex, therefore, is believed to comprise fifteen discrete extracellular domains, twenty transmembrane domains and ten cytoplasmic domains, all of which are integrated into a cellular membrane which is essential for both the structural and functional integrity of such a receptor protein. The mechanism of ligand binding

by these receptors has not been elucidated and it is definitely not attributable to one or two of the discrete extracellular domains, as is the case with immunoglobulins and T cell receptors. Because ligand gated ion channels are not structurally analogous to immunoglobulins, have never been functionally expressed as a soluble protein or on the surface of a bacteriophage as a part of a fusion protein and because the instant specification is devoid of the guidance and working examples needed to produce a functional fusion protein comprising all or part an ion channel subunit a practitioner of the art does not have a reasonable expectation of being able to make and use the claimed invention with ligand gated ion channels. See M.P.E.P. §§ 706.03(n) and 706.03(z). Further, the PCR primers described in Tables I and II on pages 17 and 18 of the instant specification appear to be critical for the practice of the instant invention. The specification does not list such primers or identify art listing such primers for any heteromeric binding proteins other than those composed of the variable heavy and light chains of immunoglobulins.

8) Claim 24 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim requires a "DNA sequence" to be expressed as a fusion protein. Whereas a DNA sequence can encode a fusion protein the instant specification does not disclose a method of expressing a DNA sequence, which is nothing more than a structural property of a DNA molecule, as a fusion protein, which is a chemical compound.

9) Claims 3, 70 and 75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention.

9.1) Claim 3 is confusing because "wherein said heteromeric receptors selected from" should be "wherein said heteromeric receptors are selected from".

9.2) Claims 70 and 75 are vague and indefinite in the recitation of the limitation "has substantially the same sequence" because it is not possible to determine at what point a similar sequence would cease to be substantially the same as a reference sequence. Specifically, one can not determine the metes and bounds of these claims in view of this limitation.

10) Claims 16 to 32 and 68 to 75 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1 to 33 and 68 to 75 of copending Application No. 08/470,297 for those reasons of record in section 8 of Paper Number 12.

11) Claims 1 to 5, 7, and 16 to 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 to 8, 16 to 21 and 23 to 33 of copending Application Number 08/349,131, now claims 1 to 32 of U.S. Patent Number 5,871,974, for those reasons of record in section 9 of Paper Number 12.

12) Claims 1 to 5, 7, 26 to 32 and 66 to 75 and 77 are rejected under 35 U.S.C. § 103 as being unpatentable over the Huse et al. publication (Science 246:1275-1281, 1989) in view of the Ladner et al. publication (WO 88/06630, 1988) and the Ladner et al. patent (5,223,409) essentially for those reasons of record as applied to claims 1 to 5 and 25 to 30 in section 14 of Paper Number 12. The Huse et al. publication described a process of producing a "combinatorial Fab expression library" of potential binding proteins in the bacteria *Escherichia coli*. The library described therein was screened for Fab molecules which could bind to a desired target by plating 30,000 phage and

making "duplicate lifts" on nitrocellulose, which were screened with labeled target protein. The Huse et al. publication did not teach the expression of the Fab proteins described therein on the surface of the bacteriophage expressing them.

Each of the Ladner et al. references taught the generation of a library of potential binding proteins and a process of screening that library of binding proteins for only those proteins having a desired binding characteristic by expressing each of those potential binding proteins on the surface of a bacteriophage encoding it. They taught that a potential binding protein would be expressed on the surface of a bacteriophage if a nucleic acid encoding that protein was fused in the appropriate reading frame to a nucleic acid within the genome of the bacteriophage genome encoded a surface protein of that bacteriophage. The Ladner et al. references expressly taught that the expression of a plurality of different potential binding proteins on the surfaces of a population of bacteriophage, in which each member of that population only expressed one species of potential binding protein would allow for the affinity purification of only those members of that population which expressed a binding protein which bound to a specific target. Because each of the binding proteins were physically attached to a bacteriophage containing a nucleic acid encoding the protein, That nucleic acid would be recovered with the protein and could then be employed in the quantitative production of the protein encoded thereby. This process is identified in the Ladner et al. patent as "directed evolution" because it involves the generation of a diverse population of molecules followed by the selection of only those members in the population having a desired characteristic. The section entitled "DESCRIPTION OF PREFERRED EMBODIMENTS" on pages 2 and 3 of the Ladner et al. WO publication expressly taught that "[a]ny protein or antibody domain for which a gene can be isolated

or constructed may be displayed in the outer surface of an organism into which the gene has been inserted" and that "[t]he organism so produced may be easily isolated from organisms which do not contain the desired gene". To have employed the directed evolution process of Ladner et al. to facilitate the rapid screening of an Fab library like that of Huse et al. to expedite the isolation of nucleic acids encoding Fab molecules having desired binding properties would have been *prima facie* obvious to one of ordinary skill in the art of molecular biology in view of this combination of references at the time that the instant invention was made. Because Huse et al. disclosed that the Fab molecules described therein were readily assemble into functional molecules within the environment of an *E. coli* cell, as were the bacteriophage of each of the Ladner et al. references, an artisan had more than a reasonable expectation that the expression of either of the antibody chains of an Fab molecule of Huse et al. as a fusion protein comprising a coat protein of a bacteriophage would result in the production of a functional Fab protein which is bound to the surface of that bacteriophage when it has been produced by the same cell that produced the Fab protein.

The Ladner et al. patent has been added to demonstrate that the express limitations of claims 66 to 75, which require two copies of gene VIII that differ from one another in nucleotide sequence, were well known in the art at the time of the instant invention. Example I beginning in column 105 of the Ladner et al. patent described the construction of an M13 cloning vector containing two genes encoding gVIII. The first gene is employed to obtain the expression of a potential binding protein on the surface of M13 bacteriophage as a gVIII fusion, and the second provides the wild-type gene VIII protein which is needed to produce structurally viable bacteriophage, as indicated by the text in lines 13 to 24 in column 113. The text in lines 27 to 31 of column 106 expressly taught that

"[s]everal silent codon changes were made" in the chimeric gVIII gene "so that the longest segment that is identical to wild-type gene VIII is minimized so that genetic recombination with the co-existing gene VIII is unlikely".

13) Applicant's arguments filed 12 August of 1999 have been fully considered but they are not persuasive.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John D. Ulm whose telephone number is (703) 308-4008. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell can be reached at (703) 308-4310.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JOHN ULM
PRIMARY EXAMINER
GROUP 1800